Neuronal Physiology following Proton Radiation Exposure

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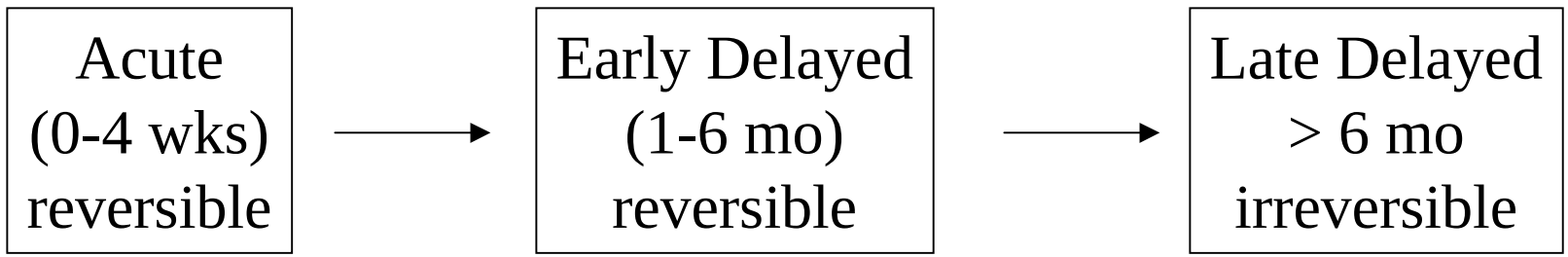
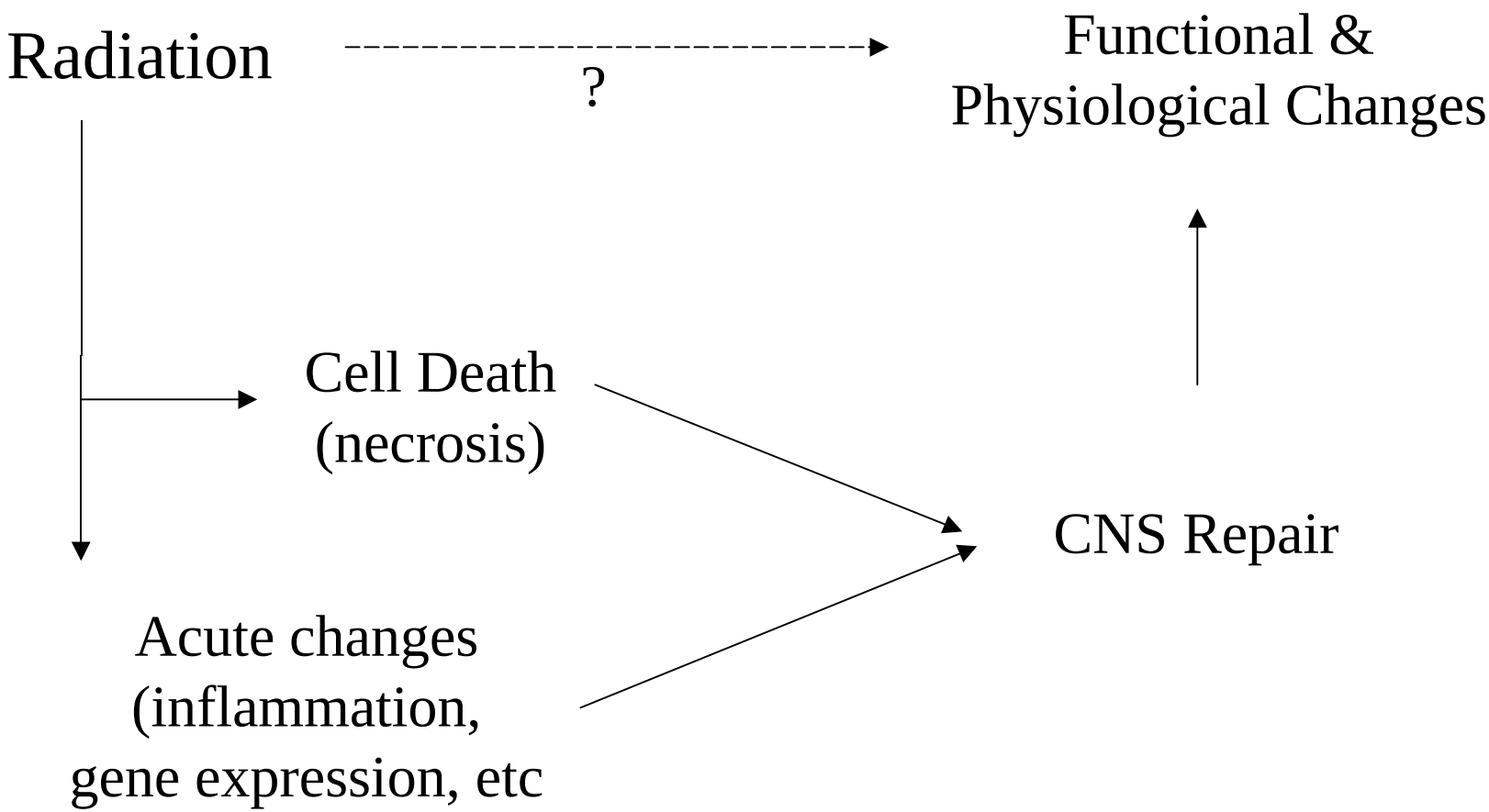
Neuronal Changes following Radiation



Tofilin & Fike, 2000

Consequences



Critical Questions?

- What are the CNS effects of proton radiation (>10 MeV)?
- How do non-neuronal cells (glial etc) interact with neuronal cells after exposure?
- Is CNS connectivity altered after radiation?
- Are there potential biomarkers or other identifiers for CNS injury after radiation?

CNS Effects of Proton Radiation?

- What are the functional consequences of radiation to neuronal populations?
- Single large dose: Bad?
  Multiple small doses: Worse?
  Time dependence of exposure?
- Critical sites within the brain that may be susceptible to radiation-induced damage?
- Are neuronal precursor cells especially vulnerable to radiation? Functional implications?

Neuronal vs. Non-neuronal?

- Differential sensitivity between neurons vs. non-neuronal cells?
- Which non-neuronal cells are most important? Microglia, astrocytes, etc.
- Speed and magnitude of response? Dose dependence? Dependent on number of neurons present?

Altered CNS connectivity?

- Are white matter tracts more important than gray matter regions?
- Neuronal reorganization? Large scale cortical remodeling vs. small regional changes?
- Functional consequences of altered connectivity?

CNS Biomarkers?

- Invasive vs. non-invasive techniques?
- Highly sensitive biomarker? With dose dependence?
  - Brain metabolites?
  - Oxygen status / consumption?
  - Metabolic needs?
- Relatively rapid, simple assay?

Potential Techniques

- Electrophysiology
  - Functional assessment of circuitry
  - Tests small group of cells
- Magnetic resonance imaging
  - Rapidly survey large brain regions
  - Anatomical, metabolic, functional imaging
  - Complimentary histology

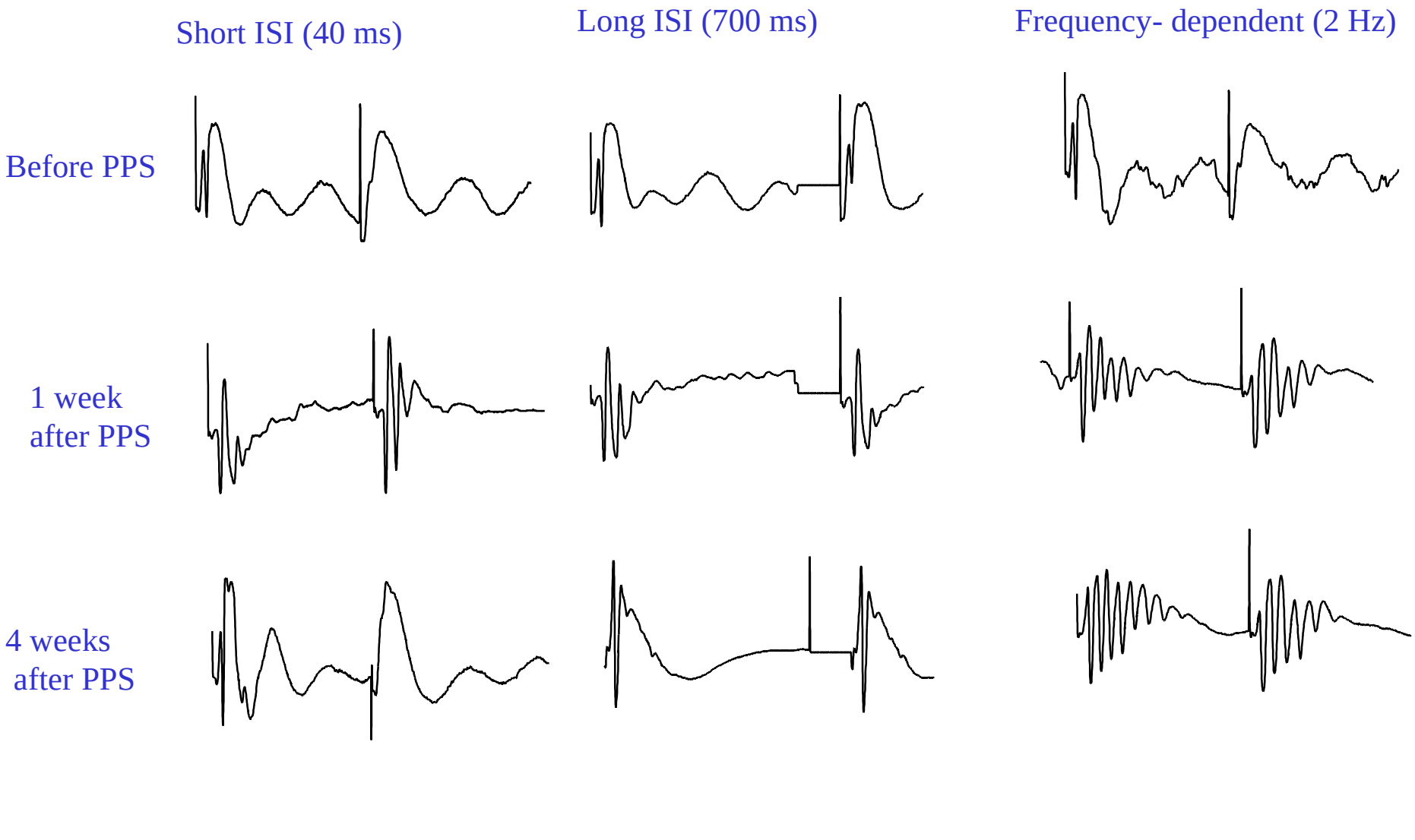
In Vivo & In Vitro Electrophysiology

- Advantages
  - Single cell or small populations (<500 cells)
  - In vitro studies examine short time periods (<24 hours) ie: acute effects
  - In vivo studies examine long time periods (>24 hours) ie: chronic changes
  - Can examine channels, synaptic and network changes

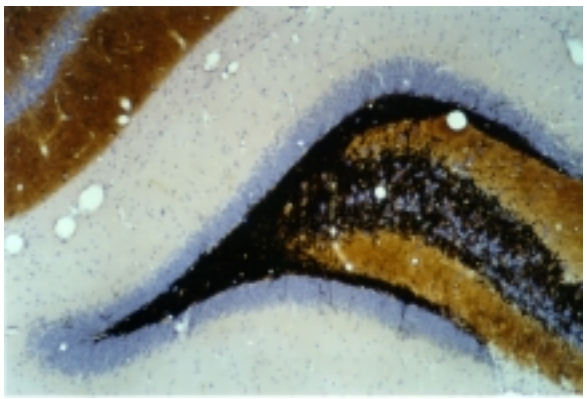
In Vivo & In Vitro Electrophysiology

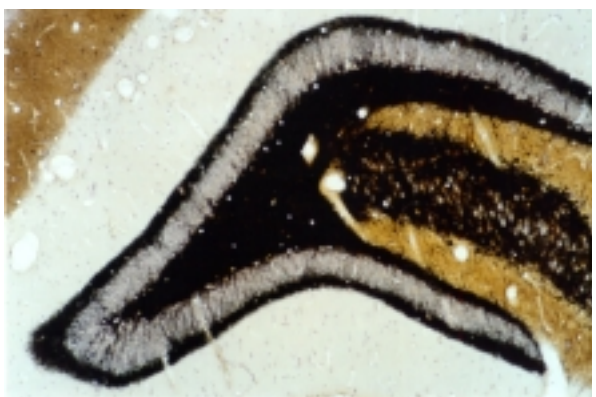
- Disadvantages
  - Examines only regional changes
  - Time consuming to perform, but excellent data
  - Requires specialized equipment (~$150K) and trained personnel
  - Need to determine which test to run

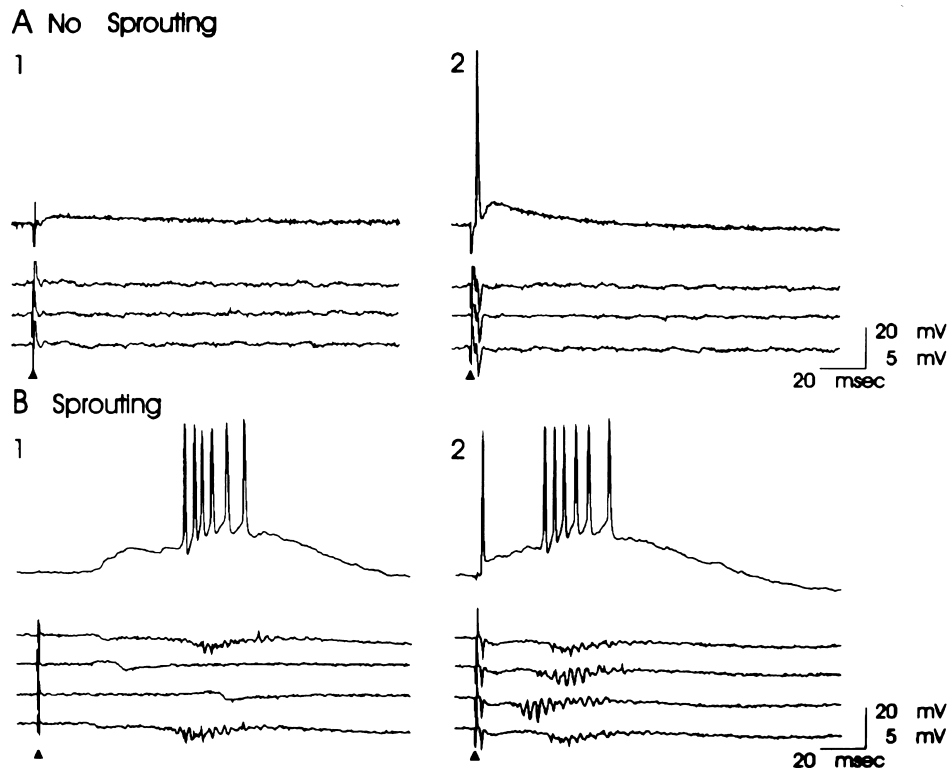
Changes in paired pulse inhibition after PPS



Synaptic Reorganization







Advantages of MRI

- “natural” reporter – protons from H_20
- non-invasive
- multiple contrast levels
- physiologically relevant time

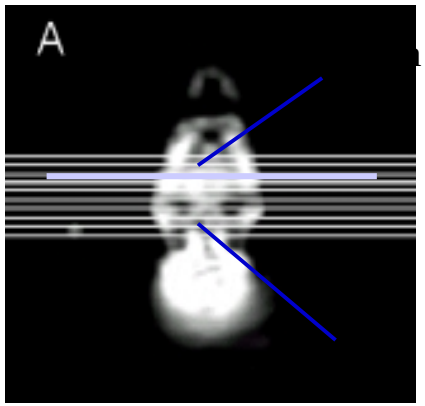
Disadvantages of MRI

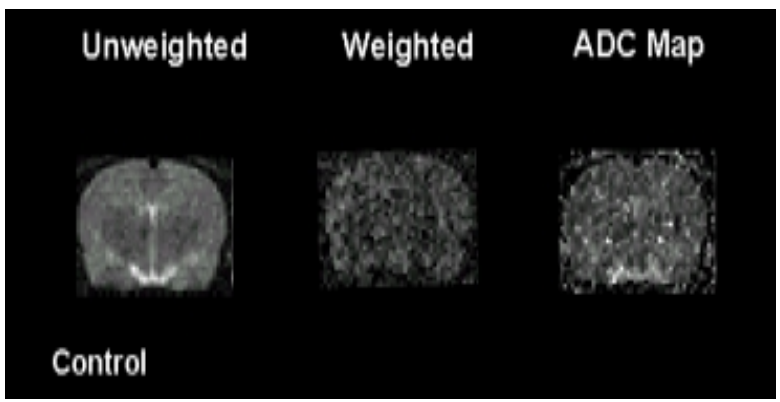
- insensitive - 10^{17} spins req'd
- skilled research/ technical personnel required
- expensive
  - 1-2 M$ to buy
  - 130K$/y to maintain

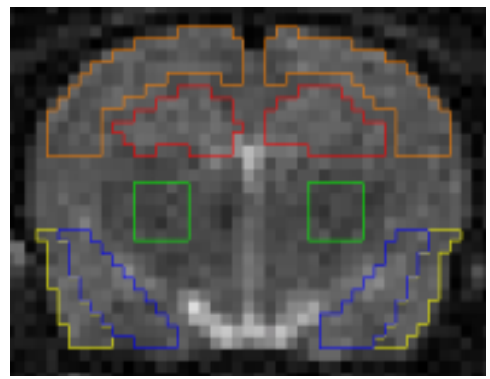
MRI Modalities

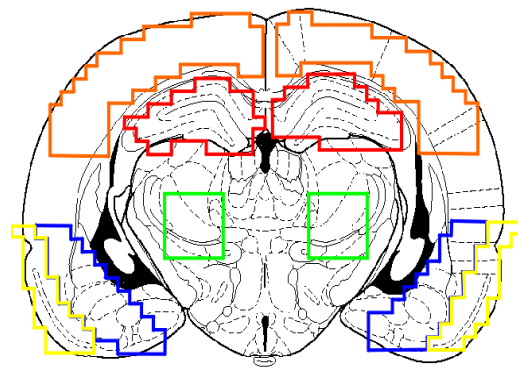
- T1 - anatomical, relaxation times
- T2 - anatomical, relaxation times
- Spectroscopy - metabolite levels
- Diffusion-Weighted - mobility of protons
- Perfusion-Weighted - blood flow
- Blood Oxygenation Level Dependent (BOLD) MRI - activity-related brain function

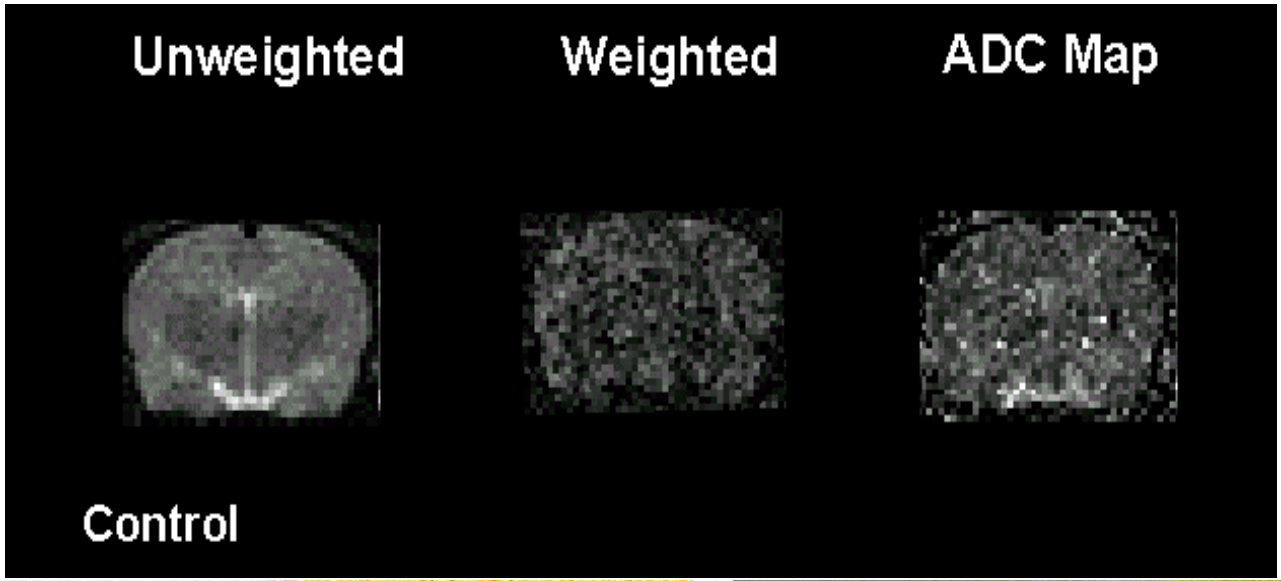
MRI Methods

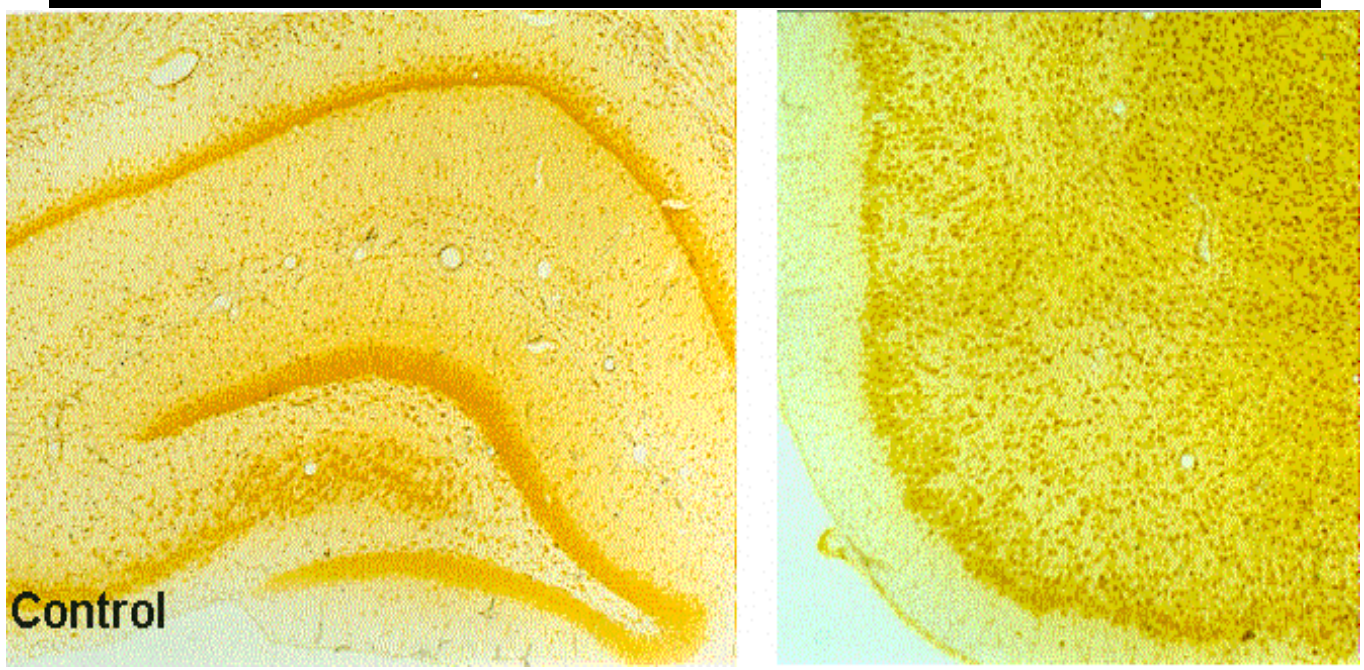


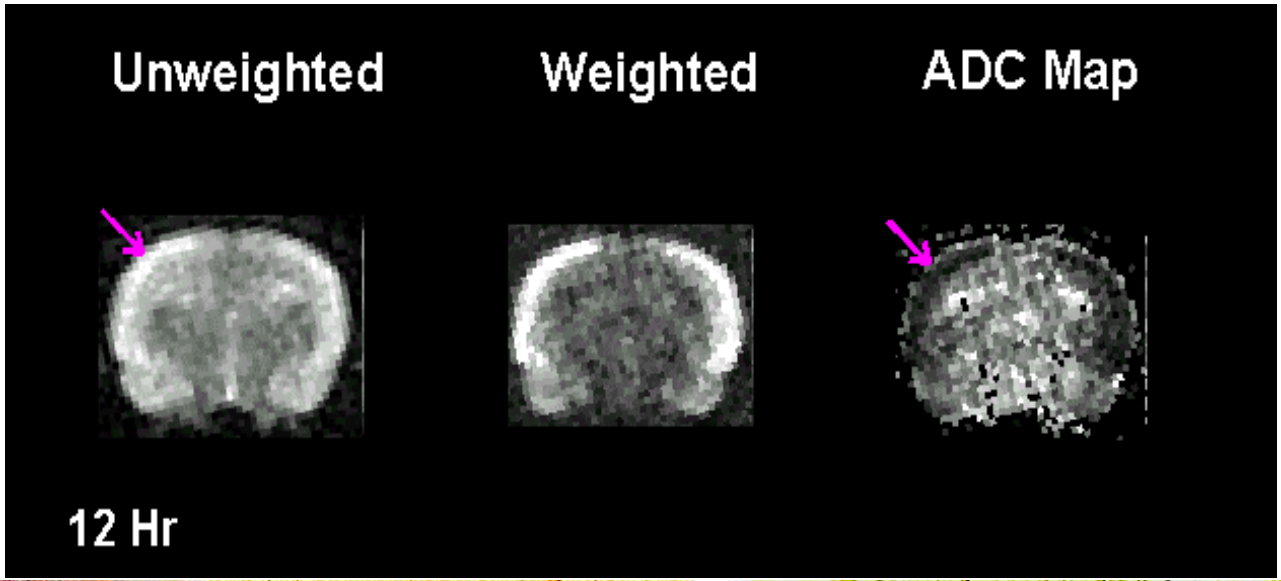






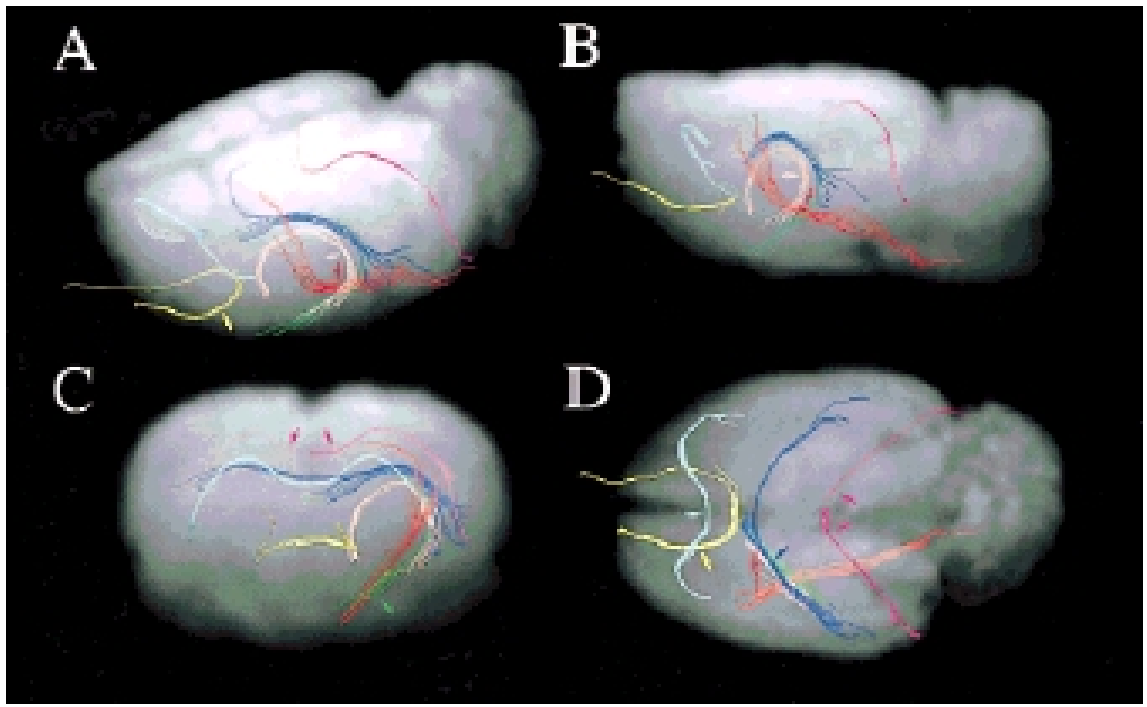

Unweighted
Weighted
ADC Map
Control


Control


Unweighted
Weighted
ADC Map
12 Hr


12 Hr

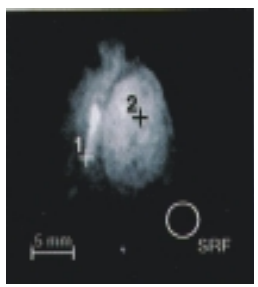
DWI Tract Tracing



In vivo 3D-fiber reconstruction for the rat brain.
Light blue: genu of corpus callosum, pink: splenium of corpus callosum, blue: fimbria, red: internal capsule, green: optic tract, peach: stria terminalis, yellow: anterior commissure.

Tumor MRI/MRS

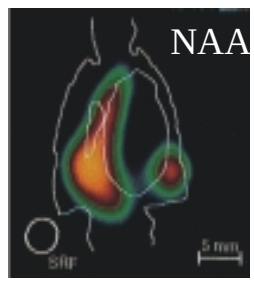
MRI

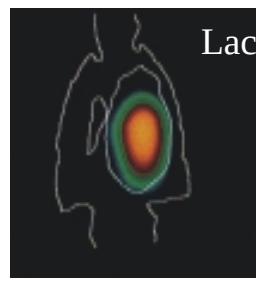


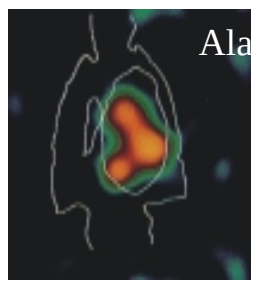
Flash Image

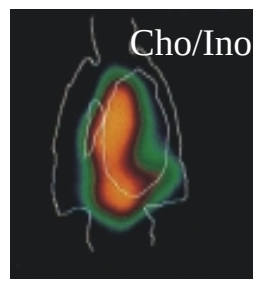
Histology

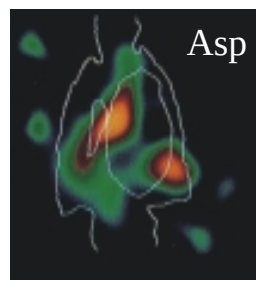
MRS Maps



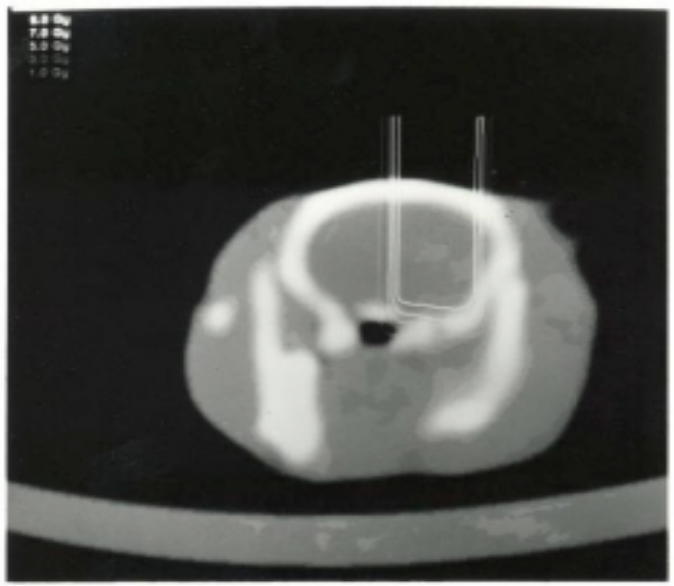








Proton Irradiation



Dr. J. Archambeau

Summary

- Obtainable short-term goals (<5 yrs):
  - Better understanding of radiation effects on CNS:
    - cellular, and
    - functional & physiological consequences
  - Sensitivity profiles of various brain regions
  - Understanding of neuronal and non-neuronal interactions?
  - Development of potential “biomarker”

Summary

- Long-term goals (>5 yrs):
  - Significance of dose(s) on CNS function
  - Long-term changes associated with radiation
    - Connectivity
    - Behavior
    - Cognition
  - Precise biomarkers with high specificity and sensitivity
  - Neurological immune responsiveness